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Novel (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles from (*E*)- and (*Z*)-3-styrylchromones: the unexpected case of (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles

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Abstract—An efficient synthetic method for the preparation of (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles has been developed. The reaction of (*E*)- and (*Z*)-3-styrylchromones with hydrazine hydrate afforded the corresponding (*E*)- and (*Z*)-4-styrylpyrazoles, respectively, saved 4′-nitro-derivatives where both (*E*)- and (*Z*)-4′-nitro-3-styrylchromones afforded (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles. The reaction mechanism for these transformations was discussed and the stereochemistry of all products was assigned by NMR experiments.

Pyrazoles are widely studied five-membered heterocyclic compounds which possess promising pharmacological, agrochemical and analytical applications.[1] In the last decade, these compounds received considerable attention since some well-known drugs such as sildenafil (Viagra) and celecoxib (Celebrex) are pyrazole derivatives.[2] Furthermore, derivatives containing pyrazole ring systems have demonstrated potent activities, such as anti-inflammatory activity,[3,4] cytotoxicity against several human cancer cell lines,[5] and inhibitory activity against monoamine oxidase which is crucial in compounds used in the treatment of Parkinson's and Alzheimer's diseases.[6] Certain 3(5)-(2-hydroxyphenyl)-pyrazoles can be used as ultraviolet stabilisers,[7] as analytical reagents in the complexation of transition metal ions,[8] as analgesic agents and platelet aggregation inhibitors,[9] and also as potent inhibitors of Hsp90 ATPase activity.[10–14]

The biological importance of pyrazole ring systems and our interest to study the reactivity of some chromones with hydrazine derivatives[15–18] prompted us to devote our attention to the reaction of 3-styrylchromones with hydrazine hydrate. It is already known that the reaction of hydrazine hydrate with chromone derivatives affords 3(5)-(2-hydroxyphenyl)pyrazoles,[9–21] and using 2-styrylchromones we have prepared a series of new 3-(2-hydroxyphenyl)-5-styrylpyrazoles.[15,16] In the present Letter, we used 3-styrylchromones[22,23] in the synthesis of new 3-(2-hydroxyphenyl)-4-styrylpyrazoles (Scheme 1).

The reactions of (*E*)-3-styrylchromones **1a–d** with an excess of hydrazine hydrate, at room temperature and under nitrogen, led to the formation of novel (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a–d** in good yields (68–87%).[24] These good results prompted us to study the reaction of (*Z*)-3-styrylchromones **2a–c** with hydrazine hydrate, which afforded the expected (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **4a–c** in 88–94% yield.[25] The same procedure was applied in the reaction of (*Z*)-4′-nitro-3-styrylchromone **2d** with hydrazine hydrate, however, the results were not as expected, the (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazole **3d** was obtained in excellent yield (98%).[26] Due to this unexpected result we decided to further explore this reaction and other (*Z*)-4′-nitro-3-styrylchromones **2e–g** were prepared[22] and left to react with hydrazine hydrate.

Keywords: 3-Styrylchromones; 3(5)-(2-Hydroxyphenyl)-4-styrylpyrazoles; NMR; Nitrogen heterocycles; Reaction mechanism.
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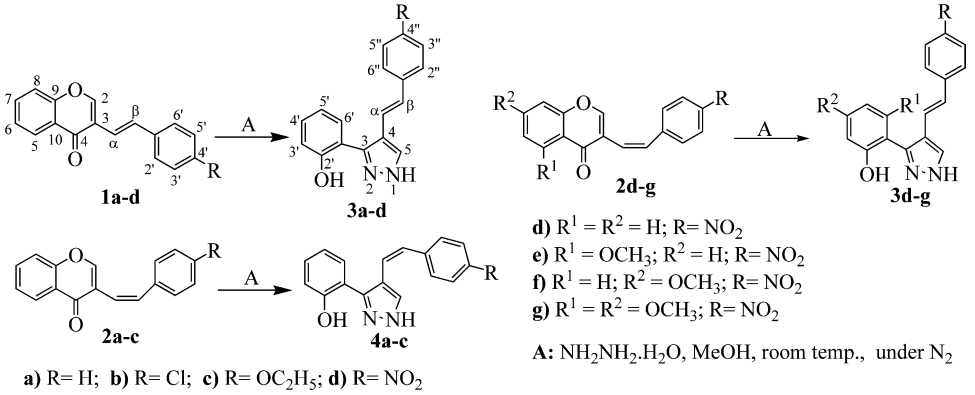
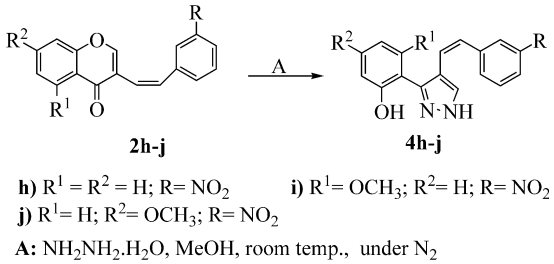


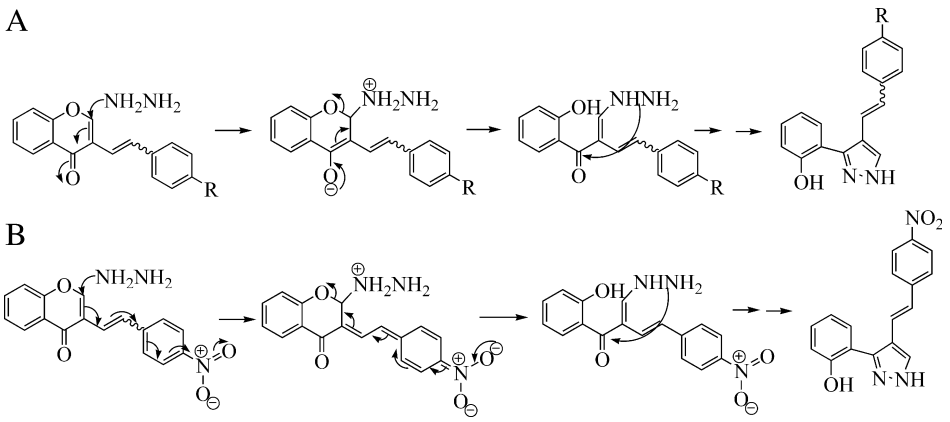
Scheme 1.

These reactions gave in all cases novel (*E*)-3(5)-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles **3e**–**g**, in very good yields (>70%). These results indicate that the 4′-nitro group has an important role in the (*Z*)→(*E*) isomerisation during the transformation of (*Z*)-4′-nitro-3-styrylchromones **2d**–**g** into the corresponding (*E*)-4-(4-nitrostyryl)pyrazoles **3d**–**g**.

The reaction mechanism of the unsubstituted or 2-substituted-chromones with hydrazine has been reported to involve a nucleophilic attack at C-2 of the chromone and consequent ring opening, followed by the intramolecular reaction between the hydrazine and carbonyl groups.[15] This seems to be the mechanism of the reaction of 3-styrylchromones **1a**–**d** and **2a**–**c** with hydrazine hydrate, which does not involve the 3-styryl group and consequently we have found that the configuration of the vinyl system is unchanged in their transformation into the corresponding (*E*)- and (Z)-4-styrylpyrazoles **3a**–**d** and **4a**–**c** (A, Scheme 2). From the results obtained with the (*Z*)-4′-nitro-3-styrylchromones **2d**–**g**, it emerged that the mechanism should be different in these cases. On the basis that nitro and carbonyl groups are considered strong electron-withdrawing groups and the nitro group could be envisaged as the more powerful one, we could envisage that after the nucleophilic attack at C-2 of the chromone nucleus the electronic conjugation should move towards the 4′-nitro-3-styryl moiety instead of the 4-carbonyl group (B, Scheme 2). This conjugate addition allowed the (*Z*)→(*E*) isomerisation of the vinylic double bond of the styryl group,[27] the most stable configuration, and consequent ring opening. The last step of this reaction mechanism is the pyrazole ring closure by an intramolecular reaction of the hydrazine and carbonyl groups. In order to confirm the proposed mechanism, we studied the reaction of (*Z*)-3′-nitro-3-styrylchromones **2h**–**j**, where there is no electronic conjugation between the 3′-nitro group and the 3-styrylchromone moiety, with hydrazine hydrate (Scheme 3). As expected (*Z*)-3(5)-(2-hydroxyphenyl)-4-(3-nitrostyryl)pyrazoles **4h**–**j**[28] have been obtained in very good yields (>80%), which confirms the proposed mechanism depicted in Scheme 2.



Scheme 3.



Scheme 2.

The NMR spectra of 3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a**–**c** and **4a**–**c** have been run in $CDCl_3$, while those of **3d**–**g** and **4h**–**j** have been acquired in DMSO-d_6 due to their insolubility in the former solvent. The main features of the ^{1}H NMR spectra of (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles (**3a**–**c** and **4a**–**c**) are the resonances of: (i) H-5 appearing as a singlet at δ_H 7.79–7.85 ppm for **3a**–**c** and δ_H 7.32–7.37 ppm for **4a**–**c**. A simple minimization of the geometries of compounds **3a** and **4a** using molecular mechanics shows that the shielding in the **4** series is due to the proximity and geometrical disposition of the phenyl ring (Pauling–Pople currents); (ii) the vinylic protons H-α (δ_H 6.84–6.85 ppm for **3a**–**c** and δ_H 6.45–6.58 ppm for **4a**–**c**) and H-β (δ_H 7.01–7.14 ppm for **3a**–**c** and δ_H 6.63–6.70 ppm for **4a**–**c**). The values of the olefinic coupling constants ($^3J_{H\alpha-H\beta}$ 11.8–11.9 Hz) in the case of compounds **4a**–**c** indicate the cis configuration for this vinylic moiety, whereas those of compounds **3a**–**c** ($^3J_{H\alpha-H\beta}$ 16.2–17.4 Hz) indicate the trans configuration. This is the main criterion to distinguish between compounds **3a**–**c** and **4a**–**c**. The ^{1}H NMR spectra of these 4-styrylpyrazoles **3a**–**c** present one deshielded broad singlet (δ_H 10.02–10.14 ppm) and those of **4a**–**c** show two deshielded broad singlets (δ_H 9.99–10.21 and 10.55–10.79 ppm) corresponding to the N*H* and 2′-O*H* proton resonances.

The ^{1}H NMR spectra of 3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3d**–**g** and **4h**–**j** in DMSO-d_6 present some characteristic resonances, namely those of H-5 appearing as a broad singlet (δ_H 8.05–8.49 ppm for **3d**–**g** and δ_H 7.71–7.74 ppm for **4h**–**j**), H-α (δ_H 6.93–7.20 ppm for **3d**–**g** and δ_H 6.26–6.45 ppm for **4h**–**j**) and H-β (δ_H 7.08–7.13 ppm for **3d**–**g** and δ_H 6.57–6.62 ppm for **4h**–**j**). The coupling constant values of the olefinic protons ($^3J_{H\alpha-H\beta}$ 16.4–17.4 Hz) of **3d**–**g** indicate a trans configuration for this vinylic moiety, while those of **4h**–**j** ($^3J_{H\alpha-H\beta}$ 11.9–12.0 Hz) support a cis configuration. These NMR spectra also present two broad singlets at high frequency values due to the N*H* (δ_H 9.76–10.27 ppm) and 2′-O*H* (δ_H 12.71–13.01 ppm) proton resonances.[29] In DMSO-d_6 solution, both 1*H*- and 2*H*-tautomers of pyrazoles **3d**–**g** and **4h**–**j** are probably present since the 2′-O*H*–N-2 hydrogen bond is broken and another is formed 2′-OH–DMSO, which are responsible for the 2′-O*H* deshielding. The broadening of the several signals in the ^{1}H and ^{13}C NMR spectra of these 4-styrylpyrazoles **3d**–**g** and **4h**–**j** confirms the existence of prototropy. The prototropy is relatively fast and average signals are observed. In order to fully characterise these compounds, we have performed these spectra in DMSO-d_6 with some drops of TFA, which increase the prototropy.

The connectivities found in the HMBC spectra of pyrazoles **3a**–**g** and **4a**–**c** (Fig. 1) allowed the unequivocal assignments of their C-3 and C-5 carbon resonances, and also the resonances of all the other quaternary carbons.

In conclusion, we have successfully applied the use of 3-styrylchromones to prepare 3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles in excellent yields and with a simple purification process. The influence of the 4′-substituent of 3-styrylchromones in this transformation was studied and it was also demonstrated that the methodology can be used to prepare (*E*)- and (*Z*)-3-(2-hydroxyphenyl)-4-styrylpyrazoles from the corresponding (*E*)- and (*Z*)-3-styrylchromones which do not have the 4′-nitro group. In this case, the reaction of both (*E*)- and (*Z*)-4′-nitro-3-styrylchromones gave only (*E*)-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)pyrazoles. Further application of this methodology for the synthesis of other 3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles will be described in due course.

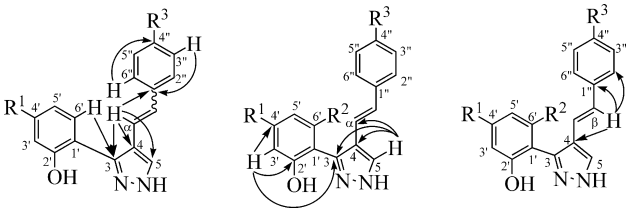


Figure 1. Main connectivities found in the HMBC spectra of **3a**–**g**, **4a**–**c** and **4h**–**j**.

Acknowledgments

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24. The procedure for the preparation of (*E*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazole **3a** is described as example: Hydrazine hydrate (0.08 ml, 1.61 mmol) was added to a solution of (*E*)-3-styrylchromone **1a** (200 mg, 8.06×10^{-1} mmol) in methanol (50 mL). The reaction mixture was stirred at room temperature, under nitrogen atmosphere, until the disappearance of the starting material. After that period, the mixture was poured into chloroform (100 mL) and washed with acidified water (2×100 mL; pH = 5). The organic layer was dried over anhydrous sodium sulphate, the solvent was evaporated to dryness and the solid residue was purified by column chromatography using chloroform as eluent. The residue obtained after solvent evaporation was recrystallised from a mixture of dichloromethane:cyclohexane. The product **3a** was obtained, as a white solid (mp 138–140 °C), in 75% yield (158.6 mg); ^{1}H NMR ($CDCl_3$): δ 6.85 (d, 1H, H-α, $J = 16.2$ Hz), 6.96 (t, 1H, H-5′, $J = 7.6$ and 7.4 Hz), 7.08 (d, 1H, H-3′, $J = 8.1$ Hz), 7.14 (d, 1H, H-β, $J = 16.2$ Hz), 7.24–7.29 (m, 2H, H–4′ and H-4″), 7.35 (t, 2H, H-3″,5″, $J = 7.7$ and 7.2 Hz), 7.45 (d, 2H, H-2″,6″, $J = 7.2$ Hz), 7.61 (dd, 1H, H-6′, $J = 7.6$ and 1.4 Hz), 7.79 (s, 1H, H–5), 10.02 (br s, 2H, N*H* and 2′-O*H*). ^{13}C NMR ($CDCl_3$): δ 116.9 (C-3′), 117.2 (C-1′), 118.5 (C-4), 118.9 (C-α), 119.5 (C-5′), 126.3 (C-2″,6″), 127.6 (C-5 and C-4′), 128.5 (C-6′), 128.7 (C-3″,5″), 129.5 (C-4″), 130.0 (C-β), 137.2 (C-1″), 147.8 (C-3), 155.6 (C-2′). EI-MS: 262 ($M^{+\cdot}$, 87), 261 (27), 245 (4), 233 (5), 216 (3), 206 (3), 189 (4), 185 (26), 171 (100), 165 (2), 155 (2), 140 (4), 131 (5), 115 (25), 102 (8), 89 (7), 77 (11), 63 (8). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.71; H, 5.60; N, 10.89.
25. The procedure for the preparation of (*Z*)-3-(2-hydroxyphenyl)pyrazole **4a** is similar to that described in Ref. 24 for pyrazole **3a**: The product **4a** was obtained, as a white solid (mp 119–121 °C), in 88% yield; ^{1}H NMR: δ 6.56 (d, 1H, H-α, $J = 11.9$ Hz), 6.70 (d, 1H, H-β, $J = 11.9$ Hz), 6.94 (ddd, 1H, H-5′, $J = 7.5$, 7.6 and 1.2 Hz), 7.06 (dd, H-3′, $J = 8.2$ and 1.2 Hz), 7.19–7.33 (m, 7H, H-2″,3″,4″,5″,6″, H-4′ and H-5), 7.84 (dd, 1H, H-6′, $J = 7.6$ and 1.6 Hz), 9.99 (br s, 1H, N*H*), 10.56 (br s, 1H, 2′-O*H*).^{13}C NMR: δ 115.5 (C-4), 116.9 (C-3′), 117.2 (C-1′), 119.3 (C-5′), 120.8 (C-α), 127.1 (C-4″), 127.3 (C-5), 128.2 (C-6′), 128.3 (C-2″,6″), 128.7 (C-3″,5″), 129.4 (C-4′), 131.3 (C-β), 137.0 (C-1″), 148.9 (C-3), 155.9 (C-2′). EI-MS: 262 ($M^{+\cdot}$, 99), 261 [$(M-H)^+$, 35], 245 (5), 233 (6), 216 (3), 206 (3), 190 (2), 185 (27), 171 (100), 165 (2), 152 (2), 140 (4), 131 (7), 115 (20), 102 (7), 89 (6), 77 (8), 63 (6). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.94; H, 5.63; N, 10.31.
26. Compound **3d** was obtained, as a yellow solid (mp 212–214 °C) in 87% yield; ^{1}H NMR (DMSO-d_6 + some drops of TFA): δ 6.93 (dt, 1H, H-5′, $J = 7.5$ and 1.0 Hz), 7.01 (d, 1H, H-3′, $J = 7.5$ Hz), 7.08 (AB, 1H, H-β, $J = 16.4$ Hz), 7.20 (AB, 1H, H-α, $J = 16.4$ Hz), 7.26–7.33 (m, 2H, H-4′ and H-6′), 7.64 (d, 2H, $J = 8.9$ Hz, H-2″,6″); 8.15 (d, 2H, $J = 8.9$ Hz, H-3″,5″), 8.19 (s, 1H, H-5). ^{13}C NMR (DMSO-d_6 + some drops of TFA): δ 116.7 (C-1′), 117.1 (C-3′), 118.2 (C-4), 120.3 (C-5′), 124.5 (C-α), 124.8 (C-3″,5″), 125.9 (C-β), 127.3 (C-2″,6″), 131.5 and 131.6 (C-4′ and C-6′), 134.1 (C-5), 142.5 (C-3), 145.1 (C-1″), 146.6 (C-4″), 155.9 (C-2″). EI-MS: 307 ($M^{+\cdot}$, 88); 306 [$(M-H)^+$, 15]; 290 (8), 277 (7), 260 (26), 244 (2), 231 (4), 215 (3), 201 (7), 191 (2), 185 (20), 171 (100), 165 (3), 152 (3), 130 (5), 115 (13), 102 (7), 89 (5), 77 (6), 63 (6), 57 (2). EI-HRMS: Calcd. for ($C_{17}H_{14}N_3O_3$) 308.1035; Found 308.1027.
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